Claims 73-81 and 83-93 are pending in this application.

Claims 73-79 are withdrawn from consideration.

Claims 80, 81, and 83-93 are rejected.

Specification - Informalities

8) (a) The use of trademarks in the instant specification has been objected to in this application. Applicants have amended the specification to capitalize the recitations in order to address the Examiner's concerns. Reconsideration and withdrawal of this specification objection is respectfully requested.

(b) Lines 12-17 on page 24 of the instant specification have been objected to for the recitations "Panel A," "Panel B," "Panel C," etc. Applicants have amended the specification to replace these recitations with - - Figure 4A - -, - - Figure 4B - -, - - Figure 4C - -, etc. to address the Examiner's concerns. Applicants respectfully request reconsideration and withdrawal of this specification objection.

Rejection(s) Maintained

21) Claims 80, 81, and 83-93 have been rejected under 35 U.S.C. §112, first paragraph, as being non-enabled with regard to the scope of the invention. Applicants respectfully disagree with this ground for rejection.

The Examiner contends that the instant claims pertaining to protective immune response are not enabled by the specification for one skilled in the art. As an initial matter, applicants have amended the instant specification on page 25, lns. 1-4 to replace "Figure 6" with - -Figure 7- - as supported by the Brief Description of the Drawings on page 8, ln. 28 – page 9, ln. 2. Further, applicants emphasize the description in Example 1, Figure 7, and the Brief Description of the Drawings for Figures 4-9, especially with reference to Lancefield's method, enable one skilled in the art to perform a bacterial assay.

Applicants disagree with the Examiner's contention as the specification provides significant data correlating the generation of anti-group A polysaccharide antibodies and bactericidal activity. In Example 1, applicants' data demonstrate that anti-group-A-streptococcus polysaccharide antibodies are protective in humans for several group A streptococcus serotypes. Applicants' data also demonstrate a significant induction of an immunogenic response in rabbits

following immunization with the GASP-TT conjugate (Example 7). Applicants have also demonstrated bactericidal activity of rabbit serum having high titers of anti-GASP-TT antibodies (Example 7). Applicants respectfully note that animal data are acceptable to show efficacy for enablement purposes in an application, see MPEP § 2164.02. In *In re Scott v. Finney*, 34 F.3d 1058 (Fed. Cir. 1994) and *In re Cross v. Iizuka*, 753 F.2d 1040 (Fed. Cir. 1985), the Federal Circuit held that animal testing was sufficient for showing a reduction to practice for human applications.

> The Board erroneously suggested that a showing of reduction to practice requires human testing in actual use circumstances for a period of time. See Engelhardt v. Judd, 54 C.C.P.A. 865, 369 F.2d 408, 410-11, 151 U.S.P.Q. (BNA) 732, 734 (CCPA 1966) (human testing of antihistamine and antiserotonin unnecessary in light of tests on laboratory animals). Reduction to practice, however, does not require actual use, but only a reasonable showing that the invention will work to overcome the problem it addresses. (In *re Scott v. Finney*, 34 F.3d 1058 (Fed. Cir. 1994)).

The Federal Circuit also found that "FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws" (In re Brana, 51 F.3d 1560 (Fed. Cir. 1995). Therefore, in view of both the human sera and rabbit data, one skilled in the art would reasonably expect the compositions of the invention to be effective to induce protective antibodies in mammals.

22) Claims 80, 81, and 83-93 have been rejected under the judicially created doctrine of obviousness-type double patenting for being unpatentable over claims 26-33 of the U.S. patent 5,866,135. Applicants respectfully disagree with this ground for rejection.

However, Applicants agree to file a terminal disclaimer upon allowance of claims in this application. The filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection. *Quad Environmental Technologies Corp. v. Union Sanitary District*, 946 F.2d 870 (Fed. Cir. 1991).

35 U.S.C. §112, Second Paragraph

23) Claims 80, 81, and 83-93 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

(a) Claim 80 has been rejected to for lacking antecedent basis for the recitation "said conjugates." Since there is an earlier recitation of a "conjugate," applicants have amended claim 80 to replace "said conjugates" with - - said conjugate - - as suggested by the Examiner. Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(b) Claim 80 has been rejected to for lacking antecedent basis for the recitations "**the** polysaccharide component" and "**the** protein component or protein fragment component," because the Examiner contends that there is no earlier recitation in the claim of any polysaccharide or protein or protein fragment "component" [Emphasis added]. Applicants have amended the claim as suggested by the Examiner by inserting the recitation - - comprising a polysaccharide component and a protein or protein fragment component- - after the limitation "polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate." Reconsideration and withdrawal of this §112, second paragraph is respectfully requested.

(c) Claim 80 has been rejected for being vague and indefinite in the recitation "protein fragment," because the Examiner contends that it is unclear as to what is encompassed by this limitation. Applicants respectfully disagree as the phrase "protein fragment" is well known in the art and clearly defined in the instant specification. The Examiner's attention is respectfully directed to page 11, lns. 24-26 and page 12, ln. 33 – page 13, ln. 1 of the instant specification where a protein fragment, or portion of a protein, "is tolerated by an individual and capable of eliciting a T-cell dependent response" and "of sufficient length, i.e. preferably at least 10 amino acids to define a T-cell epitope." Therefore, the claim is clear and definite with respect to the recitation "protein fragment." Applicants respectfully request reconsideration and withdrawal of this §112, second paragraph rejection.

(d) Claims 89, 90, and 93 have been rejected for lacking antecedent basis for the recitation "according to claim 81, wherein the conjugates," because the Examiner contends that claim 81 has antecedent support for a "conjugate." Therefore, as suggested by the Examiner,

applicants have amended the claims to recite - - the conjugate- - . Reconsideration and withdrawal of this §112, second paragraph rejection is respectfully requested.

(e) Claims 81 and claims 83-93, which depend directly or indirectly from one of the base claims identified above, have also been rejected as being indefinite due to their dependency on the rejected claims identified above. Applicants respectfully disagree. However the base claims have been amended to address the Examiner's concerns and thereby the grounds for rejection are moot.

35 U.S.C. §112, First Paragraph

24) Claims 89-91 and 93 have been rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully disagree with this §112, first paragraph rejection.

Specifically, the Examiner considers the recitation "conjugates are administered" new matter. The Examiner's attention is respectfully directed to page 11, lns. 20-27 and page 17, ln. 24 – page 19, ln. 3 where a suitable GASP conjugate comprises any protein or fragment thereof which can elicit an immune response. The instant specification supports and describes a method of eliciting a protective antibodies specific to group A streptococcal polysaccharides. Although the recitation does not present new matter, applicants have amended claim 89 to recite - -the conjugate is administered- - in order to address the Examiner's concerns regarding more than one formula I polysaccharide conjugate being administered. No new matter is introduced by the Amendment. Reconsideration and withdrawal of this §112, first paragraph rejection is respectfully requested. Applicants respectfully request reconsideration and removal of these grounds of rejection.

Applicants believe that the amendments presented herein place this case in form for allowance. However, applicants respectfully request that the Examiner call the undersigned attorney if any issues remain outstanding following consideration of this response.

AUTHORIZATION

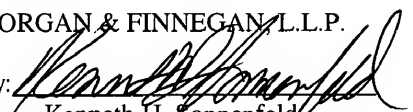
No additional fee is believed due for filing this paper. However, should any additional fee be required, the Commissioner is hereby authorized to charge any fee or credit any overpayment to Deposit Account No. 13-4500, Order No. 2016-4005US1. DUPLICATE COPY OF THIS SHEET IS PROVIDED.

In addition, the Commissioner is requested to grant a petition for any extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. 13-4500, Order No. 2016-4005US1. DUPLICATE COPY OF THIS SHEET IS PROVIDED.

Respectfully submitted,

MORGAN & FINNEGAN, L.L.P.

Dated: January 21, 2003

By: 
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Please amend the specification as follows:

IN THE CLAIMS

80. (Twice amended) A method of eliciting protective antibodies specific to group A streptococcal polysaccharide in a mammal comprising administering to a mammal a polysaccharide-protein conjugate or polysaccharide-protein fragment conjugate comprising a polysaccharide component and a protein or protein fragment component, wherein the polysaccharide component of said conjugate[conjugates] is of formula (I)

$$[\rightarrow 2)\text{-}\alpha\text{-L-Rhap-}(1\rightarrow 3)\text{-}\alpha\text{-L-Rhap-}(1\rightarrow]_n\text{-R}$$
$$\begin{matrix}3\\ \uparrow\\ 1\end{matrix}$$
$$\text{ß-D-GlcpNAc} \qquad \text{(I)}$$

wherein R is a terminal reducing L-rhamnose or D-GlcpNAc and n is a number from 3 to 50, and wherein said polysaccharide component is covalently bound to the protein component or protein fragment component of said conjugate[conjugates].

89. (Twice amended) The method of eliciting protective antibodies specific to group A streptococcal polysaccharide according to claim 81, wherein the conjugate is[conjugates are] administered with a carrier selected from the group consisting of saline, Ringer's solution and phosphate buffered saline.

90. (Twice amended) The method of eliciting protective antibodies specific to group A streptococcal polysaccharide according to claim 81, wherein the conjugate is[conjugates are] administered with an adjuvant.

93. (Amended) The method of eliciting protective antibodies specific to group A streptococcal polysaccharide according to claim 81, wherein the conjugate is[conjugates are] administered in a dosage amount of about 0.1 µg to about 10 µg per kilogram of body weight.

IN THE SPECIFICATION

Please replace the paragraph on page 7, ln. 29 – page 8, ln. 4 with the following:

Fig. 4 graphically illustrates the indirect bactericidal assay using washed human blood to which various sera were added to the tubes containing RPMI and complement as outlined in Example 1. The initial inoculum was nine CFU of group A-type 6 Streptococci. Figure 4A [Panel A] shows the growth of the organism in the rotated tubes containing normal rabbit serum. Figure 4B[Panel B] shows the growth in stationary tubes with human serum having a high ELISA titer reactive to the group A carbohydrate. Figure 4C[Panel C] shows the inhibition of growth with the same human serum as in Figure 4B[Panel B] but in a rotated tube.

On page 19, ln. 30 – page 20, ln. 9, please replace the paragraph with the following:

Sixty grams of group A streptococcal cells in 600 ml water were combined with 75 ml of 4 N sodium nitrite and 75 ml of glacial acetic acid. The solution was mixed for 15 minutes and centrifuged for 10 minutes at 11,000 rpm in a SS34 rotor. The supernatant was removed, dialyzed against water and lyophilized. The group A polysaccharide was purified from the crude lyophilized extract by gel filtration through a SEPHADEX [Sephadex] G-50 column (Pharmacia) using PBS as eluant. Fractions eluting from the column were monitored for the presence of carbohydrate using the phenolsulfuric acid assay of Dubois (31). The carbohydrate positive fractions were pooled, dialyzed at 4°C against water and lyophilized. The polysaccharide preparation (240 mg) contained less than 1% (w/w) proteins and nucleic acids. Its purity was further confirmed by ^{1}H-NMR at 500 MHz using an AM-500 BRUKER spectrometer.

Please replace the paragraph on page 20, ln. 24 – page 21, ln. 11 with the following:

ELISA Assays: The ELISA method was essentially that described by Fillit et al (18) with the following modifications. Preliminary testing with human sera indicated that 0.5 μg CHO/ ml in PBS, pH 7.2 of the liposomal preparation to sensitize the microtiter plates give the best results with minimal background readings against the liposomal control preparations.

Accordingly, 100 μl of the preparation is placed per well in microtiter plates (Dynatech plates, USA) and incubated at 37°C overnight. The plates were then washed 3x in ELISA wash buffer (10 mM NaAcetate, 100 mM NaCl, 0.1% BRIJ 35, pH 8.0 [Brij 35, ph 8.0]). The human sera was diluted in the same ELISA buffer and 100μl of a given serum dilution was placed in the plates and incubated 1 hour at 37°C. All sera were run in duplicate. After appropriate washes, 1:1,000 dilution of Goat F(ab')2 anti-human IgG (gamma chain specific) or IgM (Mu chain specific), alkaline phosphatase conjugate (Tago, Inc.,USA) was used as the secondary antibody and incubated for an additional hour at 37°C. After 3 additional washes in ELISA buffer, a phosphatase substrate (Sigma 104) in 0.1 M Diethanolamine, pH 9.6 was added to the wells, the plates incubated at 37°C for 1 hour and read on ELIDA V[Elida V] (Physica Co.) instrument at 405 nm. The titer was reported as that dilution which gave a reading of 1.0.

On page 22, lns. 16-34, please replace the paragraph with the following:

Absorption of N-acetylglucosamine antibodies from human sera: 600 μl of a 50% suspension of a N-acetylglucosamine coupled to SEPHAROSE [Sepharose] beads (Sigma Chemical Co.) in PBS was placed into a sterile EPPENDORF [eppendorf] tube and centrifuged at 4°C at 14,000 RPM for 10 minutes. The supernatant was removed and 300 μl of serum added to the beads. The suspension was rotated end over end for 1 hour at 37°C. Following a second centrifugation under the same conditions, the absorbed serum was removed and used in the bactericidal assay as described previously. To remove the N-acetylglucosamine antibodies from the affinity column, the beads containing the absorbed antibodies were packed in a 1 ml tuberculin syringe over which a solution of 0.58% (v/v) glacial acetic acid in 0.15 M NaCl, pH 2.2 is passed. The eluant is monitored by absorption at 280 nm and the peak fractions collected, dialyzed against PBS, pH 7.2, and concentrated back to the original volume of serum using an Amicon CENTRIPREP 30 [centriprep 30] concentrator (Amicon, Beverly, MA).

Please replace the paragraph on page 24, lns. 1-17 with the following:

Bactericidal Assays: Having established that human sera do contain group A carbohydrate antibodies and that the titers of these antibodies do vary in individuals, we next addressed the question of whether these antibodies would also promote opsonophagocytosis in an in vitro assay system. The bactericidal assay was essentially that used by Dr. Lancefield

(15,25,26) for testing human sera with the modifications as outlined above. Figure 4 is illustrative of the results of the phagocytic assays. Using an inoculum of nine colony forming units of a serotype 6 group A Streptococcal strain, there was a marked increase in the number of colonies in the rotated tubes in the presence of normal rabbit serum (Figure 4A[Panel A]). Figure 4B[Panel B] shows a slight increase in the stationary tube in which the human serum was used. In marked contrast, the rotated tube containing the human serum (Figure 4C[Panel C]) completely abolished the growth of the organisms (compare Figures 4B and 4C[Panel B and C]).

On page 24, ln. 30 – page 25, ln. 6, please replace the paragraph with the following:

Relationship between the Anti-CHO Titers and opsonophagocytosis by human sera: Employing the phagocytic assay, it is clear that human sera differed in their ability to promote phagocytosis of group A Streptococci. In general the phagocytic properties of a given serum correlated with the titers of the antigroup A carbohydrate antibodies. As seen in Figure 7[6], all sera exhibiting titers greater than 200,000 exhibited greater than 80% killing, while three out of the four sera with titers less than 200,000 did not. One serum with a CHO titer of 40,000 did promote phagocytosis but the degree of killing was far less than that observed with high titered anti-CHO sera.

Please replace the paragraph on page 25, ln. 31 – page 26, ln. 18 with the following:

Absorption Experiments: In an effort to determine which part of the streptococcal carbohydrate moiety was responsible for the bactericidal activity, human sera were absorbed with N-acetylglucosamine coupled SEPHAROSE [sepharose] beads as described in the methods section. Absorbed and non-absorbed sera were then used in the standard bactericidal assay. Figure 7 shows the results of these experiments. The unabsorbed serum clearly enhanced phagocytosis of the streptococci. In contrast, the serum absorbed with the N-acetylglucosamine coupled beads removed the opsonizing antibodies. As a viability control, normal rabbit serum did not enhance phagocytosis. These experiments indicate that the antibodies directed against the non-reducing terminal N-acetylglucosamine residue on group A carbohydrate were extremely

important in the opsonophagocytosis of group A Streptococci in our bactericidal assays. To confirm these results, the antibodies from selected sera which had been absorbed to the N-acetylglucosamine affinity column were eluted and used in the bactericidal assay. As also shown in Figure 9, these experiments demonstrated that N-acetylglucosamine specific antibodies eluted from the affinity column were capable of partially restoring the opsonophagocytic bactericidal activity of the serum.